Article

Human T-Lymphotropic Virus Type II Seroprevalence Among Emergency Department and Clinic Patients

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To determine the seroprevalence of human T-lymphotropic virus types I and II (HTLV-I and HTLV-II) among emergency department and clinic patients at a San Francisco, California, hospital, consecutive patients from 4 outpatient settings—emergency department, medical clinic, antenatal clinic, and neighborhood health centers—were tested for antibody to 1 of the viruses using an enzyme-linked immunosorbent assay and Western blot test. Of 4,019 patients, 169 (4.2%) had antibody to HTLV-I or -II; the seroprevalence of HTLV-II (3.5%) was greater than that of HTLV-I (0.7%). Seroprevalence for HTLV-II was highest in the emergency department (6.9%) and neighborhood clinics (3.9%) and in those aged 30 to 59 years (5.9%). Crude HTLV-II prevalence was higher in men (5.2%) than in women (2.2%), but sex was not an independent risk factor after age and location were controlled for. This study showed a higher seroprevalence of HTLV-I and HTLV-II among outpatients than did previous studies, probably because of a high proportion of injection-drug users. In view of the recent description of HTLV-II–associated myelopathy, studies of neurologic disease in this population may be warranted. HTLV-II should be included in the list of occupationally transmitted infections for hospitals with many injection-drug–using patients.

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Human T-lymphotropic virus types I and II (HTLV-I and HTLV-II) are human retroviruses sharing approximately 60% nucleotide homology. There is strong evidence that HTLV-I is the etiologic agent in adult T-cell leukemia[1-3] and in HTLV-I–associated myelopathy, a chronic demyelinating neurologic disease.[4] There is recent evidence that HTLV-II is also associated with a myelopathy similar to HTLV-I–associated myelopathy.[5-7] Infection with HTLV-I is endemic in areas of southern Japan, sub-Saharan Africa, the Caribbean basin, and the southeastern United States; the country-specific incidence rates of adult T-cell leukemia and HTLV-I–associated myelopathy show a similar geographic distribution. In the United States, the combined prevalence of HTLV-I and -II infection among volunteer blood donors has been found to be 0.02% to 0.04%,[8] and the risk factors for HTLV-I infection are a relevant ancestry or sexual contact with persons from endemic areas. Half to two thirds of cases of HTLV infection in the United States, however, have been attributed to HTLV-II,[9,10] and the principal risk factors in this case are injection-drug use,[9-13] sexual contact with an injection-drug user, and Native American ethnicity.[14-17]

A few studies have examined the prevalence of HTLV infection among emergency department patients in several US cities, motivated in part by the possible risks posed to emergency department staff. Prevalence rates of 1% to 2% for HTLV-I and -II have been reported,[18-20] and associations with known risk factors have been confirmed. There are few data on other outpatient subgroups, however. In this study we measured the prevalence of HTLV seropositivity in outpatients in emergency departments and medical, antenatal, and community clinics at a large public hospital in San Francisco, California. The intention was to obtain baseline epidemiologic data on seroprevalence among different patient subgroups to help direct the focus of future, more in-depth studies.

Patients and Methods

Subjects and Specimens

Between June 1989 and November 1990, we studied patients at four types of outpatient departments associated with San Francisco General Hospital Medical Center, namely the emergency department, general medical clinic, antenatal clinic, and two neighborhood health cen-

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ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
HTLV-I, -II = human T-lymphotropic virus types I, II

ters. Residual serum or plasma specimens that had been drawn initially for a specific medical indication were collected sequentially from the clinical laboratory of the hospital. Collection continued until about 1,000 specimens had been obtained from each location. Only information available on the specimen label, namely, age, sex, hospital number, and clinic of origin, was recorded. Duplicate specimens from the same patient were discarded by culling repeat hospital numbers. We did not gather data on the proportion of patients at each clinic who had blood specimens drawn. The study protocol was approved by the University of California, San Francisco, Committee on Human Research.

Serologic Testing

Serum from each specimen was tested with an HTLV-I enzyme-linked immunosorbent assay (ELISA; DuPont, Wilmington, Delaware). A lower ELISA cutoff threshold of 0.7 times the manufacturer's recommended cutoff was used to enhance the sensitivity of the assay for cross-reactive HTLV-II antibody, as recommended elsewhere.[21] Reactive specimens were retested in duplicate. Those with at least two out of three positive results on ELISA were then tested using a Western blot containing HTLV-I whole virus lysate plus recombinant HTLV-I p21 envelope protein (Cambridge Biotech, Rockville, Maryland). This Western blot has a sensitivity of 97.4% and a specificity of 97.5%.[22] A patient's serologic status was defined on the basis of the Western blot using the following criteria: p21env or gp46 plus p19 or p24 is seropositive; any bands less than the above criteria were classified as seroindeterminate; no Western blot bands were considered seronegative. A qualitative assessment of viral type was based on the relative intensities of the p19 and p24 bands,[23] namely, p19 of equal or stronger intensity than the p24 band equals HTLV-I; a p19 band of weaker intensity than the p24 band equals HTLV-II.

Data Analysis

Univariate and stratified frequencies were computed using a standard statistical package (SAS-PC version 6.4, Cary, North Carolina). A logistic regression analysis using the SAS PROC LOGIST function was done to estimate independent odds ratios for the various predictors of HTLV seropositivity.

Results

A total of 4,019 specimens was obtained, of which 66 lacked data on sex, 60 lacked data on age, and 1 lacked data on location. There were 1,686 (42.7%) males and 2,267 (57.3%) females, with mean ages of 44.8 years and 38.5 years, respectively (Table 1). Patients attending the medical outpatient clinic were generally older than those in the neighborhood clinics or the emergency department, whereas those attending the antenatal clinic were the youngest. Women predominated in the antenatal clinic, men in the emergency department, and the medical clinic and neighborhood clinics had more equal sex distributions.

Of 4,019 patients, 169 (4.2%) had Western blot results positive for HTLV-I or -II, and 35 (0.9%) were seroindeterminate on the Western blot test. Of specimens with ELISA reactivity greater than the manufacturer's cutoff, 89.1% were subsequently found to be positive on Western blot compared with 66.7% of specimens with optical densities between 0.7 and 1 times the cutoff. Most positive specimens were reactive to several viral proteins; only eight positive specimens had a p21env/p24-only pattern, and none had a p21env/p19-only pattern. According to the intensity of the p19 and p24 Western blot bands, 28 (0.7%) had HTLV-I antibody whereas 141 (3.5%) had HTLV-II antibody, giving a ratio of HTLV-II to HTLV-I of 4.9:1. Polymerase chain reaction analysis was subsequently done on 11 randomly selected HTLV-I– or -II–seropositive specimens from the same population. Lysates of peripheral blood mononuclear cells were amplified with primers to the common *pol* region of both HTLV types, followed by hybridization with probes to type-specific sequences within the amplified regions. One specimen hybridized to HTLV-I sequences, eight to HTLV-II sequences, and two to both HTLV-I and -II probes, suggesting either cross-reactivity or coinfection with both HTLV types. All hybridization signals were strong.

Seroprevalence for both viruses was higher among men: 0.9% for HTLV-I and 5.2% for HTLV-II, compared with 0.5% and 2.2% in women, respectively. Figure 1 shows HTLV-I and -II seroprevalence by age and sex. The

TABLE 1.—*Study Population by Clinic* and Sex†*

	Men		Women	
Clinic	*No.*	*Mean Age, yr (SD)‡*	*No.*	*Mean Age yr, (SD)‡*
Antenatal clinic	1	22 (--)	1,012	28.3 (8.8)
Medical clinic	533	49.9 (15.6)	508	52.2 (14.9)
Neighborhood clinics	373	49.0 (17.3)	492	44.9 (18.0)
Emergency department	779	39.2 (14.5)	254	39.7 (17.8)
All subjects	1,686	44.8 (16.3)	2,267	38.5 (16.9)

SD = standard deviation

*Clinic location was missing on 1 subject.
†Sex information was missing on 66 subjects.
‡Missing ages on 60 subjects were excluded from the calculation of the means.

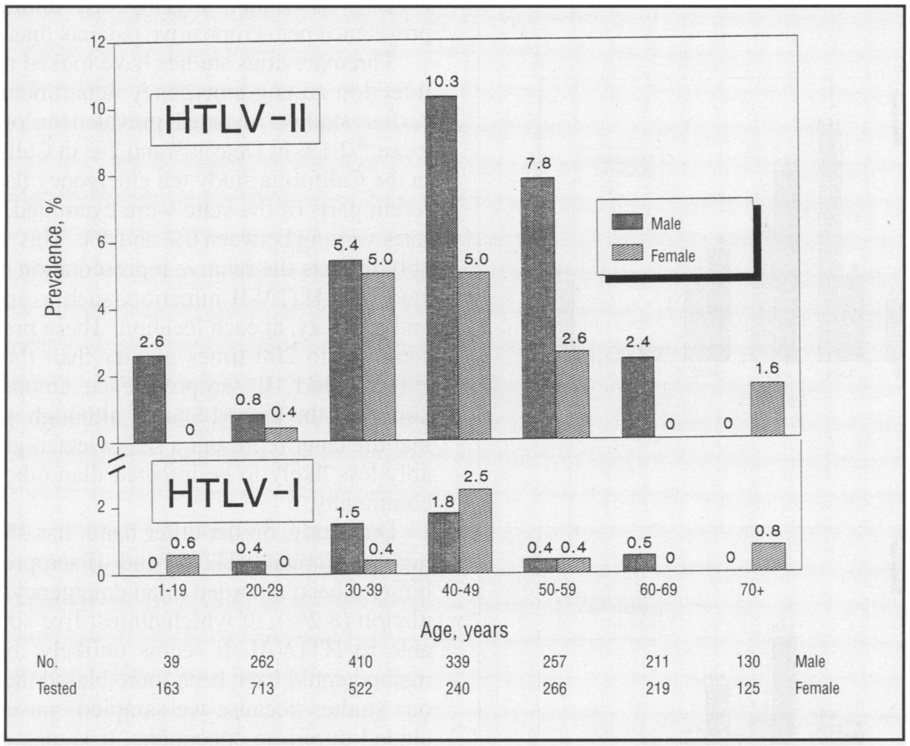

Figure 1.—The graph shows the age- and sex-specific seroprevalence of human T-lymphotropic virus types II (HTLV-II) and I (HTLV-I) among emergency department and clinic patients in San Francisco, California. The number of subjects in each age and sex subgroup is indicated across the bottom of the figure.

seroprevalence for HTLV-II was low in the youngest and oldest age groups, but reached maximum levels in the 40- to 49-year age group for men and perhaps slightly younger for women. Most of the cases of infection were accounted for by the age groups between 30 and 59 years. The seroprevalence of HTLV-I followed a similar pattern, but with lower absolute values.

The highest prevalence of HTLV-II infection was found among emergency department patients (6.9%), followed by the neighborhood (3.9%) and medical (2.3%) clinics (Table 2). Only 0.9% of those attending the antenatal clinic were seropositive for HTLV-II. To look more closely at the emergency department and neighborhood clinic populations, in which the highest prevalences occur, the data from these two locations were stratified by age and sex (Figure 2). As in the overall results, the highest age-specific prevalence of HTLV-II infection occurred in the 30- to 59-year age group in both the emergency department (10%) and in the neighborhood clinic (6.8%). Within the 30- to 59-year age group, HTLV-II seropositivity was significantly higher among women attending the emergency departments than among those attending the neighborhood clinics (12% versus 5.3%, $\chi^2 = 5.42$, degrees of freedom [*df*] = 1, $P < .02$) while for men there was little difference (9.3% versus 8.5%, $\chi^2 = 0.15$, $df = 1$,

TABLE 2.—*Human T-Lymphotrophic Virus Types I and II (HTLV-I and -II) Seroprevalence by Type of Outpatient Facility*

Location	Patients No.	No. Seropositive (%) HTLV-I	No. Seropositive (%) HTLV-II
Emergency department	1,038	13 (1.3)	72 (6.9)
Neighborhood clinic	922	8 (0.9)	36 (3.9)
Medical clinic	1,044	5 (0.5)	24 (2.3)
Antenatal clinic	1,014	2 (0.2)	9 (0.9)
All subjects	4,018*	28 (0.7)	141 (3.5)

*Data on type of facility were missing for 1 subject.

TABLE 3.—*Independent Risk Factors for Human T-Lymphotrophic Virus Types I and II (HTLV-I and -II) Seropositivity as Determined by Logistic Regression Analysis*

Variable	HTLV-I Odds Ratio	HTLV-I 95% CI	HTLV-II Odds Ratio	HTLV-II 95% CI
Age, yr				
<30	1.0	--	1.0	--
30-59	5.6	(1.3, 24.6)	10.1	(4.4, 23.2)
≥60	1.5	(0.2, 11.3)	1.7	(0.6, 5.2)
Sex				
Male	1.0	--	1.0	--
Female	1.1	(0.5, 2.6)	0.8	(0.6, 1.3)
Location				
Medical clinic	1.0	--	1.0	--
Emergency department	3.0	(1.0, 8.9)	3.0	(1.9, 5.0)
Neighborhood clinic	1.6	(0.5, 5.4)	2.1	(1.2, 3.5)
Antenatal clinic	0.6	(0.1,3.3)	0.7	(0.3, 1.5)

CI = confidence interval

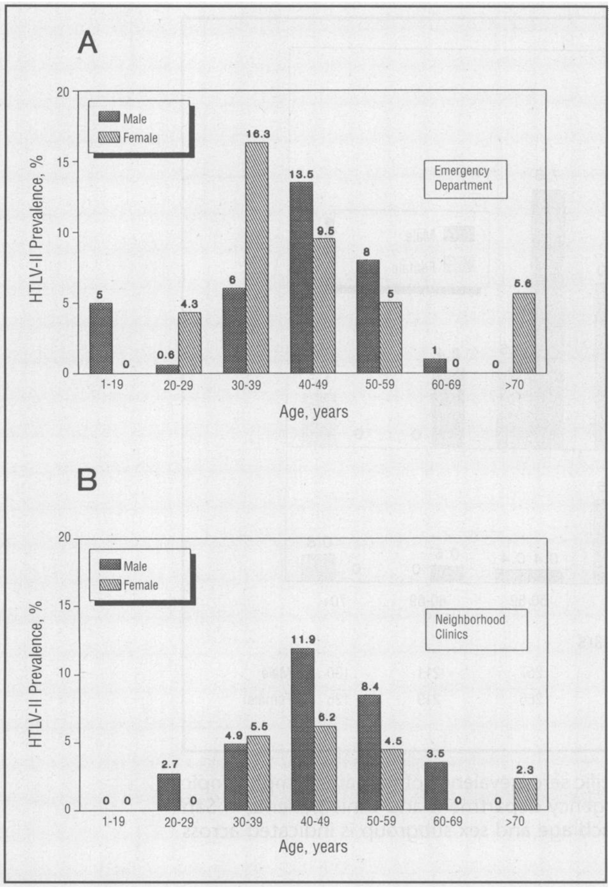

Figure 2.—The graphs show age- and sex-specific seroprevalence of human T-lymphotropic virus type II (HTLV-II) for the 2 locations with the highest prevalence within the study, namely, emergency department patients **(A)** and patients at 2 neighborhood health clinics affiliated with the same hospital **(B)**.

$P < .5$). Estimates of age, sex, and clinic-specific HTLV-I seroprevalence were less stable because of a lower overall prevalence, but a similar concentration of seropositive tests within 30- to 59-year-old emergency department patients was seen.

To obtain unbiased estimates of the risk associated with each variable under study, we did a logistic regression analysis (Table 3). Being between 30 and 59 years old and being a patient in the emergency department or neighborhood clinic were significantly associated with HTLV-II infection, but gender was not. The risk associated with HTLV-I infection differed in that neighborhood clinic attendance was not associated with seropositivity.

Discussion

In this study we tested surplus blood specimens from four types of outpatient facilities to gain an impression of HTLV-I and -II seroprevalence among San Francisco outpatients and to determine the relative prevalence of the two viruses. The latter distinction is important because HTLV-I is associated with two important diseases—adult T-cell leukemia and HTLV-I–associated myelopathy—with lifetime risks of 4%[24] and 0.24 to 2.4,[25,26] respectively. Infection with HTLV-II may also be associated with HTLV-I–associated myelopathy, although at a lower prevalence per seropositive patients than for HTLV-I.[26]

Three previous studies have looked at HTLV-I and -II infection among emergency department patients. These earlier studies revealed prevalences of 1.1% in Baltimore,[18] 2.1% in Detroit,[19] and 2% in California,[20] although in the California study ten emergency departments in different parts of the state were examined, with prevalence rates varying between 0% and 4%. This variation presumably reflects the relative representation of factors associated with HTLV-II infection, such as injection-drug use and ethnicity, at each location. These prevalence rates are some 50 to 200 times greater than the 2.5 per 10,000 HTLV-I and -II seroprevalence among random blood donors in the United States,[8] although it should be noted that the latter represent a self-selected group that is probably less likely to be infected than other sections of the community.

Our study, on the other hand, has shown a markedly higher combined HTLV-I and -II seroprevalence than has hitherto been recorded in an emergency department population (8.2%), of which almost five sixths was attributable to HTLV-II. It seems unlikely that our sampling method could have been more biased than those of previous studies because we sampled consecutively and excluded duplicate specimens. It is also possible that our serologic testing was more sensitive, especially because we specifically used a lower ELISA cutoff than recommended by the manufacturer. On the other hand, our prevalence estimate for HTLV-II may be falsely low because we differentiated HTLV-II from HTLV-I based on the HTLV-I Western blot pattern rather than by using type-specific reagents that have since become available. The most probable explanation for our findings is that our emergency department (and neighborhood clinic) populations included a higher proportion of persons with injection-drug use or other high-risk behaviors than the other studies. The demographic correlates of HTLV-II seropositivity that we observed are similar to those seen in studies of injection-drug use alone.[27,28]

With regard to antenatal clinic attenders, our finding of a 1.1% combined HTLV-I and -II seroprevalence is higher than rates of 0.26% and 0.2% reported from two studies in London in 1980 and 1990, respectively.[29,30] It is possible that our study included more women with HTLV-II–related risk behaviors of injection-drug use or sex with an injection-drug user, whereas the British studies may have included more Caribbean immigrants at risk for HTLV-I infection.

Our finding that HTLV-I and -II seroprevalence is low in young patients, greatest in the 30- to 59-year age group, and lower in the elderly is likely to be due to a combination of epidemiologic factors. First, HTLV-I and -II seroprevalence increases with age among injection-drug users, and the duration of heroin abuse rather than age itself is the strongest risk factor.[27] Persons older than 50 years who inject drugs had the highest HTLV-I and -II seroprevalence in the above-referenced study, although there were few injection-drug users of this age. Second, there may be relatively fewer injection-drug users among older outpatients in the current study because drug injection is less common among persons born before the 1930s, and those who did inject drugs are less likely to survive into older age. We also found that HTLV-II seropositivity was higher among women attending emergency departments than among those attending the neighborhood clinics (no difference among men), suggesting that women with HTLV-II risk behaviors preferentially attended emergency departments.

Emergency department staff may be at risk of occupationally acquired HTLV-II or HTLV-I, in addition to other parenterally acquired infections.[18] At least two cases of possibly occupationally acquired HTLV-I or -II infection without other risk factors have been reported, namely, one in an HTLV-I–infected Belgian midwife who worked in Africa[31] and one in an HTLV-II–infected dentist in San Francisco.[10] If we assume that the risk of acquiring HTLV infection per puncture with a blood-contaminated hollow needle is the same as the 0.2% estimate for the human immunodeficiency virus,[32] then occupationally acquired HTLV-I or -II poses a small additional risk for emergency department staff. Universal precautions against bloodborne infection should be reinforced.

In conclusion, we have demonstrated a high seroprevalence of HTLV-II and, to a lesser degree, HTLV-I among outpatients at a public hospital and its neighborhood clinics. This high prevalence is most probably a reflection of a high proportion of injection-drug use among the population studied. Because both HTLV-I and HTLV-II cause disease in a small percentage of infected persons, physicians practicing in urban America should consider HTLV-I or -II infection in their differential diagnosis of spastic paraparesis and lymphoma. Finally, infection with HTLV-I and HTLV-II should be included in existing programs for the surveillance and prevention of occupationally acquired hepatitis B, hepatitis C, and human immunodeficiency virus.

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